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Microwave Assisted Rapid Synthesis of 1-Arylpiperazines.

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MICROWAVE ASSISTED RAPID SYNTHESIS OF 1-ARYLPIPERAZINES.

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Abstract : 1-Arylpiperazines, an important class of compounds were synthesized rapidly under Microwave irradiation from diethanolamine and substituted anilines using Pollard's method of synthesis. The yields obtained were comparable with the conventional yields and drastic reduction in reaction time was observed.

1-Phenylpiperazine derivatives possess antihypertensive, adrenolytic, antihistaminic and antiinflammatory properties.[1] They bind with high affinity to serotonin sites.[2-5] They were also found to possess antipsychotic activity.[6]

Prelog, Driza and Blazek reported the synthesis of 1-Arylpiperazines from bis-(2-chloroethyl)amine and substituted anilines.[7] Pollard and MacDowell have reported another method of synthesis whereby the hydrochlorides of diethanolamine and aniline were heated at about 240° for a period of eight hours.[8] Some derivatives of arylpiperazines were prepared by Pollard and Wicker.[9] Hans Wynberg et al. have reported a convenient synthesis of 1-Aryl-4-methylpiperazines by reaction of aromatic ethers with N-lithio-N′-methylpiperazine.[10]

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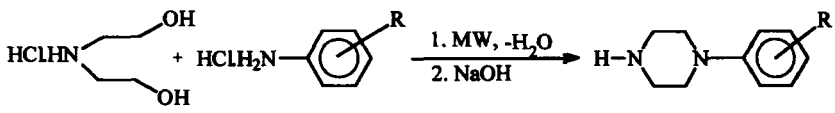
Microwave heating offers many advantages over conventional forms of heating. Due to the mass heating effect, much faster temperature increase can be obtained. High temperatures required for reactions are achieved rapidly. The applications of MW energy in organic chemistry are increasing rapidly[11-13] since the papers of Giguere[14] and Gedye.[15]

We report here the synthesis of 1-Arylpiperazines under MW irradiation using Pollard's method. The reaction was a good candidate for MW assistance as the reactants, i.e hydrochlorides of aniline and diethanolamine being polar, couple effectively with MW radiation. Sublimation and polymerization could be controlled by adjusting the time programming for MW radiation. A modified domestic Microwave oven was used for our reactions. A glass assembly was specially designed to connect the reaction flask to a condensor connected through a hole made at the rear wall and a Dean- Stark apparatus fixed outside the MW oven. The completion of the reaction was monitored by the amount of water collected in the Dean-Stark apparatus. The reaction time reduced drastically and the yields obtained were comparable with those obtained by the conventional method.

Scheme



Experimental : The oven operates on duty cycles, hence lower power settings mean long intervals between zero and full power, instead of some truly intermediate power.

1-Phenylpiperazine : Aniline, (0.22 mol, 20.5g), diethanolamine, (0.20 mol, 21g) were taken in 100 mL round bottom flask and carefully neutralized with 50 mL of conc. HCl with cooling. The excess water was removed by distillation. The mixture was then irradiated in the MW oven (KELVINATOR T-37, 700 Watts output) for

Table

R	Net MW exposure time (mins.)	Isolated Yield (%)	Conventional Yield[Ref.9] (%)	Observed B. P. °c/mm	Reported[Ref.9] B. P. °c/mm
H	12	50	50	105-108/1	156-157/10[Ref.8]
2-CH_3	8	20.6	26.5	102-104/1	136.5-137.5/10
3-CH_3	21	50.3	22.8	112-114/1	154.2-156.2/10
4-CH_3	8	22	25.5	110-111.5/1	150.9-152.5/10
2-Cl	14	18.5	32.7	98.5-100/1	133.9-134.9/5
3-Cl	11.5	28	38.4	139.5-141/1	157.2-158.2/5
4-Cl	8	45.4	52.3	137-138.5/1	155.7-157.2/5 (M.P.71.5-73.5)

1-Arylpiperazines obtained were characterized by their boiling points and PMR spectral data.

6 mins at full power and then for 20 mins. at 30% power to control sublimation. The net irradiation time was 12 mins. The water evolved collected in the Dean-Stark apparatus. The mixture was then neutralized with NaOH to give a dark coloured oil which was separated from the aqueous layer. The aqueous layer was extracted with $CHCl_3$ and the $CHCl_3$ extract was combined with the organic layer. The organic phase was washed several times with water to remove excess NaOH. It was then dried over sodium sulfate and $CHCl_3$ was distilled out. The residual oil was subjected to vacuum distillation to give an oil distilling at 105-108°C/1mm which weighed 16.3g (50% yield).

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